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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PAK, JOHN D	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 06/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/713,498	ZHAO, CHAOYING	
	Examiner	Art Unit	
	JOHN D PAK	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-22,25,27,28 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,22,25 and 27* is/are rejected.

7)☒ Claim(s) *21,28 and 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims **20-22, 25, 27-28 and 30** are pending in this application.

It is noted for the record that upon reconsideration and review of the state of the art upon a search update and new search, several new references are deemed to be particularly relevant. New grounds of rejection are deemed to be necessary. The finality of the Office action of 11/4/03 is hereby withdrawn.

This application has been examined under an election of species requirement wherein the elected and examined subject matter has been any combination of sodium chloride and hydroxyethyl starch. See the Office action of 3/19/03. Accordingly, the claims here will be examined to the extent that they read on NaCl + hydroxyethyl starch.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 20 is rejected under 35 U.S.C. 102(b) as being anticipated by Kramer et al. (US 4,908,350).

Kramer et al. explicitly disclose hyperosmotic and hyperoncotic, physiologically acceptable (i.e. directly injectable) solutions for treating patients experiencing or threatening to experience hypodynamic shock (column 2, lines 33-37; column 3, lines 14-19). Kramer's solutions comprise a crystalloid and a colloid, wherein the crystalloid is preferably sodium chloride (column 3, lines 29-37). The concentration of the

crystalloid is between about 1800 to 3000 mOsm (column 3, lines 43-45; see claim 1). It is noted that 1800 mOsm NaCl is about 5.3 w/v% NaCl, and 2400 mOsm NaCl is about 7 wt/v% NaCl. The colloid has an average molecular weight that is higher than about 30,000 and lower than 400,000, preferably lower than 100,000 (column 3, lines 46-51). Suitable colloids include hydroxyethyl starches, dextran and gelatins (column 3, lines 51-52; see claim 5) The concentration of the colloid is selected so as have the colloidal osmotic pressure of higher than 30 mm Hg, preferably about 70 mm Hg, which is equivalent to about 6% Dextran (column 3, lines 59-60; column 4, lines 60-63). The following solutions are explicitly exemplified:

1.2 M NaCl[1] + 6 wt/v% dextran 70 in deionized, sterile water (column 4, lines 60-63);

1.2 M NaCl + 15 w/v% dextran 40 in deionized, sterile water (column 6, lines 9-36);

1.2 M NaCl + 6 w/v% hydroxyethyl starch in deionized, sterile water (column 6, lines 11-36).

Further, different hyperosmotic NaCl solutions were also used with 6% dextran 70, including 1200 mOsm and 1800 mOsm NaCl (see column 6, lines 36-41). It is noted that 1200 mOsm converts to about 3.5 wt/v% NaCl, and 1800 mOsm converts to about 5.3 w/v% NaCl. Various other 2400mOsm solutions are disclosed (column 7, Table III).

[1] 1.2 M NaCl is about 7 w/v% NaCl.

Claim 20 is thereby anticipated, because every element of the claimed feature is explicitly disclosed by Kramer et al. In this regard, the Examiner is interpreting applicant's claim language "sodium chloride in an amount between about 1.5% and 6.9% (w/v)" to include Kramer's 1.2 M NaCl, which is about 7 w/v%, as well as 1800 mOsm NaCl, which is about 5.3 w/v% NaCl.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20, 22, 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kramer et al. (US 5,443,848, hereinafter, Kramer '848) in view of Kramer et al. (US 4,908,350, hereinafter, Kramer '350).

Kramer '848 explicitly disclose compositions that are useful for small volume rapid restoration of oxygen consumption and oxygen delivery in severely hemorrhagic individuals (column 3, lines 25-28). The composition contains a mixture of sodium acetate (NaAc) and sodium chloride (NaCl), wherein the relative concentrations of the two components are about 2-7 osmolar parts of NaAc and 1-3 osmolar parts of NaCl, including for example 5:3, 7:1 or 6:2 (NaAc:NaCl) in osmolar basis. See column 3, lines 41-50. Total osmolarity in excess of 500 mOsm, such as 1000 mOsm or 2400

mOsm is disclosed (column 5, lines 6-8; claims 6-7). Formulation as an injectable solution is disclosed (e.g., column 7, lines 22-40). Use with colloids such as dextran or hydroxyethyl starch or crystalloid such as glucose is disclosed (column 5, lines 30-36). With dextran, 4-8 wt% is disclosed (e.g., claim 5).

Kramer '350 disclose compositions for use in treating hypodynamic shock such as resulting from hemorrhage (column 3, lines 65-68). The composition comprises a crystalloid and a colloid, wherein the crystalloid is preferably sodium chloride (column 3, lines 29-37). The concentration of the crystalloid is between about 1800 to 3000 mOsm (column 3, lines 43-45; see claim 1). It is noted that 1800 mOsm NaCl is about 5.3 w/v% NaCl, and 2400 mOsm NaCl is about 7 wt/v% NaCl. The colloid has an average molecular weight that is higher than about 30,000 and lower than 400,000, preferably lower than 100,000 (column 3, lines 46-51). Suitable colloids include hydroxyethyl starches, dextran and gelatins (column 3, lines 51-52; see claim 5) The concentration of the colloid is selected so as have the colloidal osmotic pressure of higher than 30 mm Hg, preferably about 70 mm Hg, which is equivalent to about 6% Dextran (column 3, lines 59-60; column 4, lines 60-63).

The difference between the claimed invention and Kramer '848 is that Kramer '848 does not use applicant's parameters to describe their compositions, but Kramer '848 clearly suggests the same composition now claimed by applicant, based on the parameters disclosed and converting them to correspond to applicant's parameters.

The parameter of Kramer '848, wherein the osmolarity is in excess of 500 mOsm such as right above 500 mOsm, 1,000 mOsm and 2400 mOsm, equate to slightly above about 1.45 w/v% NaCl, 2.9 w/v% NaCl and 7 w/v% NaCl, respectively. Taking into account the fact that this osmolarity is being contributed by NaCl, NaAc, and to a small part by the colloid additive, one having ordinary skill in the art would have obviously recognized that, for example, in a 2400 mOsm solution in Kramer '848 invention, only 600 osmole is available from NaCl when the osmolar ratio of NaAc to NaCl is 6:2. Thus, the 600 osmole NaCl is equivalent to 300 mM NaCl, which is equivalent to about 1.75 wt% NaCl.

Such recognizable calculations for a person having ordinary skill in this art would have shown that the disclosure of Kramer '848 teaches a concentration range for NaCl that is well within the concentration range claimed by applicant.

As for applicant's claim feature that the total sodium ion concentration is less than or equal to an equivalent amount of sodium ion from a 6.9 w/v% NaCl solution, such feature is clearly encompassed by Kramer '848 since by definition, a 2400 mOsm composition by Kramer '848 cannot exceed sodium ion concentration that would be present from about a 7 w/v% NaCl solution – taking into account that Kramer '848 has NaAc to further significantly contribute to the osmolarity and sodium ion concentration, one having ordinary skill in the art would have plainly recognized applicant's claim feature as having been met by the disclosure of Kramer '848.

Kramer '848 teaches addition of colloids such as hydroxyethyl starch or dextran. While specific amount of hydroxyethyl starch is not expressly disclosed, one having ordinary skill in the art would have been motivated to arrive at a suitable amount of the hydroxyethyl starch, which would have been within applicant's claimed amounts, from the following prior art teachings:

1) Dextran, an alternative colloid to be used for the same function in the composition, is used by Kramer '848 at amounts ranging between 4-8 wt% (claim 5);

2) Kramer '350 teaches that the amount of the colloid should be such that the colloidal osmotic pressure of higher than 30 mm Hg is achieved, for example, with 6% dextran (column 3, lines 59-60; column 4, lines 60-63).

3) Kramer '350 teaches that the colloids have an average MW that is higher than about 30,000 and lower than 100,000, preferably.

Hence, one having ordinary skill in the art would have been taught that hydroxyethyl and dextran of similar MW are being used, and since similar MW colloids would have been expected to provide similar colloidal osmotic pressure, operative concentration amounts for dextran would be approximately equivalent to operative concentration amounts for hydroxyethyl starch. Therefore, the ordinary skilled artisan would have been motivated to utilize an amount of hydroxyethyl cellulose that is at least covered by the 4-8 wt% used for dextran, given the interchangeability of dextran and hydroxyethyl in providing the colloidal functionality in Kramer '848 and Kramer '350.

Applicant recites in claim 22 that at least 10% of the hydroxyethyl starch has MW between 25000 and 45000. It is the Examiner's position that in the absence of criticality of such a feature that provides unexpected results, MW range distribution would have been within the skill of the ordinary skilled artisan. Given Kramer '350's teaching that MW of 30,000-1000,000 is suitable, one having ordinary skill in the art would have been motivated to select MW of, for example 30,000, which would appear to meet applicant's claim feature. Such MW distribution feature is a manufacturing and product parameter that the ordinary skilled artisan would have been able to select when choosing the appropriate hydroxyethyl starch substance. With a 30,000 average MW hydroxyethyl starch, for example, at least 10% between 25,000-40,000 would have been a reasonable distribution requirement, given the physiological grade required for Kramer's inventions. Therefore, one having ordinary skill in the art would have been motivated to choose an average MW and the MW distribution characteristic as claimed, with the expectation that such features would deliver the colloidal properties as taught by the teachings of Kramer et al. (both references).

The method of preparing claims, claims 25 and 27, are noted, but the amount of the composition components have already been addressed, supra, and one having ordinary skill in the art would have mixed the components at such proportions in several alternative orders to formulate a suitable injectable composition.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/08500 for the reasons of record.

Applicant's arguments of 4/8/04 have been fully considered. Applicant will note that only claim 20 is maintained in this ground of rejection.

Applicant argues that because the added L-arginine in WO 98/08500 would vasodilate the brain, it would be expected to lower the ability of a hypertonic saline solution to elevate the blood pressure in a patient experiencing hypotensive shock, which applicant argues, would appear to increase the NaCl content in the composition. Thus, applicant argues, L-arginine materially affects the basic characteristics of a hypertonic saline solution.

The Examiner cannot agree with applicant's arguments. Applicant is reminded that the claims are given the broadest reasonable interpretation during prosecution. The invention that is *claimed* requires nothing more than a "pharmaceutical composition." Therefore, applicant's arguments are misdirected in the first place. The

Examiner maintains that, without more, the basic and novel charcteristic of a "pharmaceutical composition" is not materially affected by L-arginine.

Moreover, given that WO 98/08500 teaches hypertonic formulations that treat hemorrhage and trauma, it cannot be understood how having L-arginine "materially affects the basic characteristics" of a pharmaceutical composition. Even if L-arginine does all that applicant asserts, how does that change the fact that hemorrhage and trauma are treated, just like applicant's invention aims to do.

Applicant's argument is deemed unpersusasive. The rejection of claim 20 is maintained. Rejection of all other claims over this reference is withdrawn in view of applicant's arguments.

Claims 21, 28 and 30 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims **and** ensuring that the actual weight amounts recited in claim 28 operate to further define the percentages set forth in the independent claim 20 (e.g. include final volume feature such as, "wherein the total volume of the composition is 1000 ml").

Applicant's attorney is invited to telephone the Examiner in the interest of expediting the further prosecution of this application.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620, effective February 3, 2004.** The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Thurman Page, can be reached on (571)272-0602, effective February 3, 2004.

The fax phone number for the organization where this application or proceeding is assigned is (703)872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

JOHN PAK
PRIMARY EXAMINER
GROUP 1600